IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: William J. Curatolo et al.		
SERIAL NO.: 09/770,562	Examiner:	B. Fubara
	Art Unit:	1618
FILED: January 26, 2001		
FOR: Solid Pharmaceutical Dispersions With Enhanced Bioavailability		

Commissioner for Patents
Washington, D.C. 20231

Sir:

DECLARATION UNDER 37 CFR 1.132

I, Scott B. McCray, declare that:

1. I was awarded the degree of Bachelor of Science in Chemical Engineering in 1979 by the University of California-Los Angeles, a degree of Master of Science in Chemical Engineering in 1981 by the University of California-Los Angeles, and subsequently awarded a Ph.D. in Chemical Engineering in 1984 by the University of California-Los Angeles. I have been employed by Bend Research, Inc., of which I am also part owner, up to the present time. My title is Director of Membrane Development.

2. Bend Research, Inc. is part-owned by Pfizer, Inc., the Assignee of the above-identified application.

3. I am familiar with the instant patent application. I have read the Office Action which was mailed May 17, 2006, and am aware of the rejection of claims 1, 7, 11, 13, 15, 23-26, 38-39, 41-43, 45, 47, and 49-52 under 35 USC 103(a) as being unpatentable over Miyajima et al. (US 4,983,593, "Miyajima") as set forth therein.

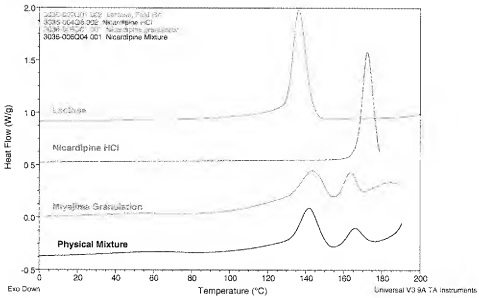
4. Under my supervision, a granulation of nicardipine hydrochloride, HPMCAS-LF, and lactose was made following the method outlined in Example 6 of Miyajima. To prepare the granulation, 1 g nicardipine hydrochloride and 3 g HPMCAS-LF were dissolved in 25 mL acetone. Next, 7.5 g lactose was dispersed into the solution. The solution was stirred in a fume hood at room temperature for 1 hour, and then dried under vacuum for 1 hour. The resulting dry composition was in the form of a brittle yellow wafer. The dried composition was then granulated using a mortar and pestle. The Miyajima granulation comprised nicardipine hydrochloride, HPMCAS, and lactose in the mass ratio 1:3:7.5.

5. The Miyajima granulation was examined using modulate differential scanning calorimetry (DSC) as follows. Pans containing the samples were crimped and sealed at ambient temperature and humidity, then loaded into a Thermal Analysis Q1000 DSC equipped with an autosampler. The samples were heated by modulating the temperature at ± 0.796°C/min, and ramping at 5°C/min to about 200°C. In addition to the Miyajima granulation, the following samples were analyzed by DSC using the above procedure: (1) nicardipine hydrochloride, (2) lactose, and (3) a physical mixture of nicardipine hydrochloride:HPMCAS:lactose in a mass ratio of 1:3:7.5.

6. Figure 1 shows the results of the DSC experiments. The baselines of the scans have been shifted relative to each other to allow the results to be viewed separately in the same figure. The Miyajima granulation and the physical mixture both show two melt peaks corresponding to crystalline material: one at about 140°C corresponding to crystalline lactose, and one at about 165°C corresponding to crystalline nicardipine hydrochloride. (The melt peaks in the Miyajima granulation and in the physical mixture are shifted slightly relative to the pure lactose and pure nicardipine hydrochloride samples.) In contrast, a solid amorphous dispersion of amorphous drug molecularly dispersed in a polymer would show a single thermal event corresponding to the glass-transition temperature of the dispersion. The presence of a melt peak corresponding to

nicardipine hydrochloride indicates the presence of crystalline drug in the Miyajima granulation. These results demonstrate that the composition formed using the process of Miyajima does not result in a solid amorphous dispersion of amorphous nicardipine molecularly dispersed in HPMCAS.

Figure 1. DSC Results

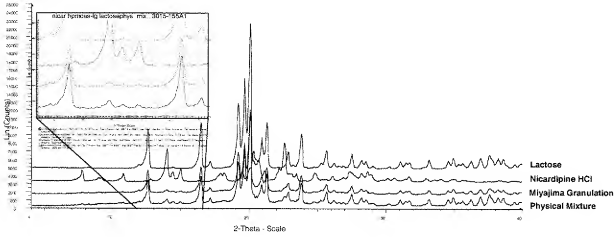


7. The Miyajima granulation was also examined using powder x-ray diffraction (PXRD) using a Bruker AXS D8 Advance diffractometer. Samples (approximately 100 mg) were packed in Lucite sample cups fitted with Si(511) plates as the bottom of the cup to give no background signal. Samples were spun in the φ plane at a rate of 30 rpm to minimize crystal orientation effects. The x-ray source (KCu_{α}, $\lambda = 1.54$ Å) was operated at a voltage of 45 kV and a current of 40 mA. Data for each sample were collected over a period of 30 minutes in continuous detector scan mode at a scan speed of 2 seconds/step and a step size of 0.04°/step. Diffractograms were collected over the 2θ range of 4° to 40°.

8. Figure 2 shows the results of the PXRD analysis. The baselines of the patterns have been shifted relative to each other to allow the patterns to be viewed separately in

the same figure. The physical mixture and the Miyajima granulation both exhibited a pattern showing two sharp peaks in the region of 13° to 15° 2θ (not present in lactose; see inlay) that are characteristic of crystalline nicardipine hydrochloride. Comparison of the intensity of these two peaks in the Miyajima granulation sample and the intensity of the corresponding two peaks in the physical mixture (in which the nicardipine was 100% crystalline) indicates that the nicardipine in the Miyajima granulation is about two-thirds crystalline, the remainder apparently amorphous.

Figure 2. PXRD Results



9. These results demonstrate that the composition made using the method of Miyajima resulted in the formation of crystalline drug. Thus, the composition made using the process of Miyajima is not a solid amorphous dispersion of amorphous drug molecularly dispersed in HPMCAS.

10. An *in vitro* test was performed to evaluate the concentration-enhancement provided by the granulation of Miyajima. For these tests, the granulation was added to microcentrifuge tubes in duplicate. Tests were conducted at two different concentrations of material. For one set of tests, a sufficient amount of material was added so that the concentration of drug would have been 200 μg/mL, if all of the drug had dissolved (theoretical maximum supersaturated concentration, "Theoretical MSSC").

For a second set of tests, the theoretical MSSC was 2000 μg/mL. The tubes were placed in a 37°C temperature-controlled chamber, and 1.8 mL PBS (pH 6.5 and 290 mOsm/kg) was added to each respective tube. The samples were quickly mixed using a vortex mixer for about 60 seconds. The samples were centrifuged at 13,000 G at 37°C for 1 minute. The resulting supernatant solution was then sampled and diluted 1:6 (by volume) with methanol and then analyzed by high-performance liquid chromatography (HPLC). HPLC analysis was performed using an Agilent RX-C_{18} column at 30°C, with a mobile phase of 65/35 (vol./vol.) 0.15%TFA, 0.05% TEA/ acetonitrile. UV absorbance of each sample was measured at 290 nm. The contents of each respective tube were mixed on the vortex mixer and allowed to stand undisturbed at 37°C until the next sample was taken. Samples were collected at 4, 10, 20, 40, 90, and 1200 minutes.

11. In addition to the Miyajima granulation, a spray-dried dispersion of the present invention consisting of 25 wt% nicardipine hydrochloride in HPMCAS-MG (made per the Friesen Declaration previously submitted), was tested under the same conditions. Also tested was crystalline nicardipine hydrochloride.

12. The concentrations of drug obtained in these tests were used to determine the maximum supersaturated concentration of drug ("MSSC"). MSSC, the C_{90} (concentration of drug at 90 minutes), and the C_{1200} (concentration of drug at 1200 minutes) are shown in Table 1. The spray-dried dispersion of the present invention and crystalline nicardipine hydrochloride alone are also shown in Table 1 for comparison.

Table 1

Sample	Theoretical MSSC (μg/mL)	MSSC (μg/mL)	C_{90} (μg/mL)	C_{1200} (μg/mL)
Miyajima granulation	200	64	64	46
Spray dried dispersion	200	127	89	127
Crystalline nicardipine	200	12	12	12
Miyajima granulation	2000	197	196	197
Spray dried dispersion	2000	166	135	166
Crystalline nicardipine	2000	28	13	14

13. As described in paragraph 8, the Miyajima granulation sample contains about 1/3 amorphous nicardipine and about 2/3 crystalline nicardipine. Thus, the test at the higher theoretical MSSC (2000 μg/mL) is equivalent to dosing about 667 μg/mL of amorphous nicardipine. The test at a theoretical MSSC of 200 μg/mL is equivalent to dosing about 67 μg/mL amorphous nicardipine and about 133 μg/mL crystalline nicardipine. The results in Table 1 are consistent with this interpretation. At the higher theoretical MSSC, there is sufficient amorphous nicardipine for the composition to provide a MSSC value of about 197 μg/mL. However, when the Miyajima granulation was dosed at the lower theoretical MSSC (200 μg/mL) there was only about 67 μg/mL amorphous nicardipine, such that the composition only provided a MSSC value of 64 μg/mL. By comparison, the spray-dried dispersion of the present invention, when dosed at a theoretical MSSC of 2000 μg/mL provided about the same MSSC value as the Miyajima granulation—166 μg/mL. However, at the lower theoretical MSSC (200 μg/mL), the spray dried dispersion of the invention provided a MSSC value of 127 μg/mL—more than twice that of the Miyajima granulation. These results are consistent with the spray dried dispersion of the invention being completely amorphous and the Miyajima granulation being only 1/3 amorphous.

14. These results show that the spray dried dispersion of the invention is superior to the Miyajima granulation and would be expected to have superior performance *in vivo*. This is because as drug is absorbed from the gastro-intestinal tract, and nicardipine dissolves to replace it, the spray-dried dispersion of the invention would maintain the dissolved nicardipine concentration at a high level, as it is all amorphous. In contrast, for the Miyajima granulation, after the amorphous drug was dissolved, the concentration of dissolved nicardipine would be expected to drop to the solubility of crystalline nicardipine—about 12 μg/mL—as only crystalline nicardipine is left.

15. In addition, the test at a lower MSSC is more physiologically relevant. Nicardipine is supplied in 20 mg and 40 mg capsules. As a human gastro-intestinal volume is on the order of 200 mL in the fasted state, the concentration of nicardipine

dosed to the *in vivo* use environment would be about 100 to 200 μg/mL. Thus, the test at a theoretical MSSC of 200 μg/mL is more physiologically relevant than the test at 2000 μg/mL.

16. Finally, it should be noted that the Miyajima granulation contained only 8.7 wt% nicardipine, while the spray-dried dispersion contained 25 wt% nicardipine. However, the spray-dried dispersions of the present invention show higher enhancement of dissolved drug concentration at lower drug loading in the dispersion. Accordingly, a spray dried dispersion containing 8.7 wt% nicardipine would be expected to show even higher MSSC values than those obtained by the spray dried dispersion containing 25wt% nicardipine.

17. In summary, the granulation made by the method of Miyajima does not result in the formation of a solid amorphous dispersion of amorphous nicardipine molecularly dispersed in HPMCAS, and the Miyajima granulation does not provide the concentration enhancement obtained with the spray dried dispersions of the present invention.

18. I further declare that all statements made herein of my own knowledge are true and that all statements made on information are believed to be true; and further that these statements were made with the knowledge that willful false statements and the likes made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Respectfully submitted,

Oct. 11, 2006
Date

Scott B. McCray